REMARKS/ARGUMENTS

This amendment is submitted in connection with the submission for Request for Continued Examination (RCE), and is responsive to the Final Office Action dated April 6, 2004, and Advisory Action dated August 10, 2004. Reconsideration of the above identified application is respectfully requested.

Prior to the submission of the RCE, the undersigned counsel for Applicants had a telephone interview with Examiner Lewis, which took place on August 31, 2004, to discuss the Advisory Action. Particularly, the undersigned disagreed with the Examiner's characterization of Applicants' invention as if Applicants are claiming nothing more than adding water to the excipient to replace the residual solvent entrapped in the excipient with water, followed by drying to remove the replaced water from the excipient so as to produce a low-residual-solvent excipient.

In fact, Applicants' way of removing the residual solvent from the excipient is by adding a solvent/water solution to the excipient which contains no more than 40% by volume of water to replace the residual solvent in the excipient with water. This is in fact highly unusual and should qualify as "unexpected results" because they actually adding more solvent into the excipient in exchange for the replacement of solvent with water. The undersigned has drawn the Examiner's attention to a diagram shown on page 13 of the application, in which an isopropanol/water solution containing 90% by volume of isopropanol and 10% of water is added to the sodium starch glycolate (SSG). The addition of such a high volume of isopropanol to the excipient did not increase the solvent content of the excipient. Rather, it removes the residual solvent from the excipient.

The undersigned further pointed out to the Examiner that contrary to his argument, the addition of water or a water solution containing high volume of water to the excipient not only could not remove the residual solvent from the excipient, but only would damage the excipient and make it unsuitable for use in pharmaceutical preparation.

The Examiner, therefore, recommended that Applicants submit a 132 declaration to disclose their findings regarding the solvent removal effects between the use of water or a water solution and the use of a solvent/water solution containing high volume of solvent in the excipient Applicants thank the Examiner for the suggestion.

In light of the Examiner's suggestion, a 132 declaration signed by one of the inventors is attached herein to this submission.

In the Final Office Action dated April 6, 2004, the Examiner requests that Applicants cancel claims 28-29.

In response to this suggestion, claims 28-29 has been canceled.

In addition, the Examiner alleges that claims 28-34 have been misnumbered, and should renumber as claims 30-36. However, since the original claims 28-29 have been cancelled, there is no need to move the originally added claims 30-34 to claims 32-36. Therefore, Applicants decide to leave the previously added claims 30-34 with the same numbers. The Examiner is welcome to discuss the renumbering matter with Applicants' counsel any time should he believe that the numbering should be done in other way.

In addition to the cancellation of claims 28-29, Applicants have converted claim 6 into an independent claim, which particularly claim the excipient as chitosan.

Applicants further amended claim 1 by adding the process of making the low-residual-solvent excipient into the claim so as to convert it into a product-by-process claim. Furthermore, claim 13, the method claim, is amended to further clarify the invention. No new matter has been introduced.

Claims 1-10, 12-20, and 26-27 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Gala et al. U.S. 5,478,571 (Gala) in combination with Bai U.S. 5,840,329 (Bai). Claims 30-36 (which in view of this response, stays as claims 28-34) are rejected under under 35 U.S.C. § 103(a) as being unpatentable over Gala in combination with Bai, and further in view of Bahia et al. U.S. 6,075,177 (Bahia).

Applicants respectfully submit that the amendments of claims 1 and 2 have overcome the rejections for the reasons set forth in the following sections.

Claims 35-36 (which in this case stay as claims 33-34) are further rejected under 35 U.S.C. § 112, second paragraph, as being indefinite because the term "water absorbing property" is not defined. Due to the amendment of claim 1, Applicants respectfully submit that this issue is moot.

Rejections – 35 U.S.C. § 103(a)

Claims 1-10, 12-20, and 26-27 are rejected under 35 U.S.C. . § 103(a) as being unpatentable over Gala et al. U.S. 5,478,571 (Gala) in combination with Bai U.S. 5,840,329 (Bai).

Specifically, the Examiner alleges that "Gala teaches methods to remove residual solvent alcohols without adverse affects **to the drug** by **adding a small amount of water** (col. 2, lines 24-30) ….. Gala teaches that the excipient blend of **conventional** carrier materials can be

lactose, microcrystalline cellulose and cornstach (col. 3, lines 28-33)." (emphasis added); (See Final Office Action at page 3-4,¶ 8). In addition, the Examiner alleges that "Bai teaches that carboxymethylcellulose and sodium starch glycolate, polysaccharide with water-absorbing properties (*i.e.*, containing $-CH_2$-O-R-COO^-A^+ moieties), are known as inert pharmaceutical excipients." Thus, the Examiner concludes that "[i]t would have been obvious to one of ordinary skill in the art to use the method of Gala to reduce the residual solvent content of **any known drug/excipient system**. Therefore, a skilled artisan would have been motivated .... to use any known **conventional excipient** .... in the method provided by Gala to obtain the low-residual-solvent excipient claimed in the present invention. Further, **the choice of solvent and reaction conditions**, *i.e.*, temperature and agitation methods, are seen to be a choice of experimental design, are well known to one of ordinary skill and are well within the purview of the prior art." (emphasis added); (See Final Office Action at pages 5-6. ¶ 8).

At the outset, Applicants would like to state for the records that neither Gala nor Bai has taught a low-residual-solvent excipient with less than 3000 ppm. Also, the method taught by Gala does not include mixing an excipient possessing a water absorbing property with a solvent/water solution containing no more than 40% by volume of water. And, it would NOT be obvious to one of ordinary skill in the art to add a solvent/water solution to an excipient in hope for a reduction in residual solvent from the excipient, because it is against the norm to add more solvent into a system with the expectation that the residual solvent entrapped in the system can be driven out.

This is further substantiated by the 132 declaration submitted with this amendment. In the 132 declaration, the inventor has described that the addition of water would in fact make the

excipient pasty and losing fluidity, which in turn would make the excipient unsuitable for use in preparation of pharmaceuticals, fish foods, plant growth regulators, pesticides and/or herbicides. Thus, in essence, Applicants' claimed invention, in both the amended claim 1, which incorporated the process of making the low-residual-solvent excipient into the claim, and the amended claim 13, which is amended to further clarify the invention, is in fact "teaching away" from Gala, and may constitute "unexpected results" departing from Gala's teaching. It is well established that "unexpected results" negate any obviousness arguments. Thus, clearly Applicants' claimed invention is not obvious over Gala in view of Bai.

Please note that the amended claims 1 and 13, a limitation which recites "a solvent/water solution which contains no more than 40% by volume of water" is added. This is supported by the specification, such as lines 13-15 of page 13, the examples, and claims 15-17, as originally filed. No new matter has been introduced.

Applicants further incorporate by reference their earlier responses to this arguments.

Additionally, Applicants respectfully traverse the Examiner's arguments for the following reasons:

First, the foremost and most obvious distinction between Gala and the claimed invention, as agreed upon by Applicants and the Examiner, is that Gala discloses a drug composition or a formulation containing a water-insoluble drug (See col. 2, lines 22-24 and lines 35-41) and an excipient blend of **conventional pharmaceutical carrier materials** consisting of lactose (65-70% w/w), microcrystalline cellulose (15-25% w/w) and corn starch (8-12% w/w) (See col. 3, lines 29-34); and Applicants' claim an excipient with low residual solvent per se.

In Gala, the water-insoluble drug is required to be first dissolved in an organic solvent so as to facilitate the uniform dispersion of the drug among the excipients. As described by Gala, "[t]here exist many water-insoluble drugs which must be dissolved in organic solvents in order to uniformly disperse them throughout an inert carrier material. Obviously however, once the dispersion has been carried out, the organic solvent must be removed whereby the dissolved drug becomes solidified as particulate matter within the matrix system." (See col. 2, lines 35-41). Thus, it is clear that the goal of Gala is to remove the excess solvent from the drug, NOT from the excipients, which is contrary to Applicants' invention, where the focus is on the removal of the residual solvent that is left within the excipient. An excipient is defined as "any more or less inert substance added to a prescription in order to confer a suitable consistency or form to the drug; a vehicle." (See Dorland's Illustrated "Medical Dictionary", 26th Edition, B.W. Saunders Company). Thus, clearly it is not a drug and shall not be generalized as a drug composition or drug/excipient system, as characterized by the Examiner in his argument regarding Gala. In fact, there is no limitation that Applicants' excipient must be used with either water-soluble or water-insoluble drug. Thus, in the case a water-soluble drug is involved, Gala's invention is not even applicable. Therefore, Gala is not an analogous art to Applicants' claimed invention and should not be considered to be prior art for the purpose of establishing obviousness.

Secondly, Applicants' excipient is NOT a conventional excipient, while Gala clearly teaches the use of conventional excipients, which effectively has "taught away" from Applicants' claimed invention. Applicants claim a low-residual-solvent excipient, which is characterized by its containing of less than 3000 ppm of solvent and possession of water absorbing property.

The Examiner's citations of col. 2, lines 24-30, col. 3, lines 45-57, and col. 3, lines 28-33, of Gala to support his contention that Gala teaches an excipient containing less than 3000 ppm of solvent is misplaced. As acknowledged by the Examiner, Gala teaches a drug carrier blend (*i.e.*, drug/excipient system), NOT an excipient alone. Even if a drug carrier blend contains less than 3000 ppm of solvent, it does not mean that each of the excipients in the drug carrier blend contains less than 3000 ppm of solvent.

Furthermore, a conventional excipient, by definition, is an excipient that can be readily bought in the market. At the present time, no conventional excipients except the ones manufactured by Applicants, as indicated in Table 3 of the application, contain less than 3000 ppm of solvent. For example, the conventional market products for sodium starch glycolate, as illustrated in Table 3 of the present application on page 12, include EXPLOTAB® (which contains 41712/498 ppm of residual ethanol/ethyl acetate); PRIMOJEL® (which contains 20299 ppm of residual ethanol); TABLO® (which contains 4575 ppm of residual ethanol); VIVASTAR® P 5000 (which contains 346/10175 ppm of ethanol/methanol); VIVASTAR® (which contains 5666 ppm of methanol), all contain residual solvent more than 3000 ppm. And the reason why these excipients contain high-residual-solvent, even though the solvent is hazardous to human health, is simply because the solvent embedded in the sodium starch glycolate is difficult to be removed. Thus, the Examiner has not fulfilled his burden of proving a *prima facie* case that a "conventional" excipient used in Gala contains, as alleged by the Examiner, less than 3000 ppm of solvent.

The method cited by the Examiner to support his assertion that Gala teaches methods to remove residual solvent alcohols is also false. (See col. 2, lines 24-30). As stated above, Gala

never teaches the addition of a solvent/water solution containing no more than 40% by volume of water to an excipient possessing water-absorbing property can remove the residual solvent from the excipient.

In addition, the methods disclosed by Gala are designed to remove solvent altogether from a drug/excipient system, NOT from the excipient per se. The Examiner has not fulfilled his duty of proving that the same methods used by Gala to remove the solvent from the drug/excipient system can be used to remove solvent from the particular excipient alone. In fact, judging from the fundamental structural and physical differences between the drug used in Gala, which is water-insoluble, and the excipient claimed by Applicants, which possesses water absorbing property, it does not appear that the solvent removal principle used in Gala can be applied to the excipient claimed by Applicants.

Additionally, the Examiner's argument that "the choice of solvent and reaction conditions [in Applicants' claimed invention], *i.e.*, temperature and agitation methods, are seen to be a choice of experimental design, are well known to one of ordinary skill and are well within the purview of the prior art," is without merits. To establish a *prima facie* case of obviousness under 35 U.S.C. § 103(a), the prior art reference must teach or suggest all the claim limitations. *See* M.P.E.P. § 706.02(j), citing In re Vaeck, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991). Thus, it does not matter whether an ordinary skill in the art's choice of experimental design is, if the element(s) taught in the claim is completely missing in the prior art, the Examiner has not fulfilled his burden of establishing the *prima facie* case.

Since neither Gala nor Bai teaches the use of a solvent/water solution containing no more than 40% by volume of water, and in fact, Gala has taught away from adding any solvent/water

combination by suggesting the addition of water, NOT solvent/water solution, to the drug blend mixture, the choice of solvent and reaction conditions become irrelevant to the obviousness inquiry, and thus shed no light to the obviousness determination.

Finally, as acknowledged by the Examiner, Gala does not disclose each of the particular polysaccharide claimed or excipients with water-absorbing properties (See Final Office Action at page 4). Without knowing the water-absorbing properties of the excipient, the Examiner is now asking an ordinary skill in the art to guess or conduct undue experimentation to determine the solvent ratios and/or reaction conditions, which is definitely not a reason in determining obviousness.

The Examiner's citation (col. 8, lines 12-39) of Bai in support of his notion that polysaccharides with water-absorbing properties (i.e., containing CH_2-O-R-COO^-A^+ moieties), are known as inert pharmaceutical excipients is also misplaced. The two paragraphs of Bai cited by the Examiner teach nothing but conventional binders. Nothing about excipient with less than 3000 ppm of solvent, or water-absorbing property, is mentioned in these two paragraphs. Applicants invite the Examiner to particularly point out where his notion of polysaccharides with water-absorbing properties can be found in the excerpts.

Because (1) none of Gala and Bai teaches a low-residual-solvent excipient (particularly containing less than 3000 ppm of solvent and possessing water-absorbing properties), and (2) none of Gala and Bai teaches the addition of a solvent/water solution containing no more than 40% by volume of water to be used in removing the residual solvent from the excipient, Applicants' claimed invention is not obvious over Gala in combination with Bai. Applicants respectfully request that the rejections be withdrawn.

Rejections – 35 U.S.C. § 103(a)

Claims 30-36 (*i.e.*, present claims 30-34 due to cancellation of the previous claims 28-29) are rejected under 35 U.S.C. § 103(a) as being unpatentable over Gala in combination with Bai and further in view of Bahia. Specifically, the Examiner alleges that "[n]either Gala nor Bai explicitly teach the synthesis of low-residual-solvent excipient (*i.e.*, synthesis of carboxymethylcellulose). However, their synthesis is well-known in the art as shown by Bahia." (See Final Office Action at page 8). Additionally, the Examiner asserts that "Bahia teaches that carboxymethylcellulose is prepared by reacting cellulose with a strong alkali and with monochloroacetic acid or a salt thereof (col. 3, lines 11-13; col. 4, lines 5-16)." (See Final Office Action at page 9).

As shown in the previous section, *supra*, the combined teachings of Gala and Gai do not teach a low-residual-solvent excipient containing less than 3000 ppm of solvent and possessing water-absorbing properties, and also do not teach a process of making the low-residual-solvent excipient containing the use of a unique combination of solvent and water solution. The addition of Bahia does not bridge the gap by providing the missing elements of Applicants' claimed invention. Especially, Bahia is an unanalogous art. It teaches carboxymethlcellulose filaments as tow or strand of textile filaments at least 15 mm long or a fabric of textile filaments at least 3 mm long. (See Abstract of Bahia). It does not teach carboxymethylcellulose to be used as an excipient, and certainly it does not concern about the reduction of the residual solvent in the excipient. In fact, as shown in col. 3, lines 23-25, the preferred solvents for producing the cellulose filaments are tertiary amine N-oxides, which is not used in Applicants' claimed

invention (*i.e.*, claims 13, 16 and 17). Because the combination of Gala, Bai, and Bahia do not teach all of the claimed elements, Applicants' claimed invention is not obvious over Gala, Bai, and Bahia. Applicants respectfully request that the Examiner withdraw the rejections.

In view of the foregoing, the rejections have been overcome and the claims are in condition for allowance, early notice of which is requested. Should the application not be passed for issuance, the examiner is requested to contact the applicant's attorney to resolve the problem.

Respectfully submitted,

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